Human Research Program
Health Human Countermeasures Element

Evidence Book

Risk of Risk of Therapeutic Failure Due to Ineffectiveness of Medication

March 2008

National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

TABLE OF CONTENTS: CHAPTER 21

I. PRD Risk Title: Risk of Therapeutic Failure Due to Ineffectiveness of Medication

Description: Based on subjective reports, drugs are effective during spaceflight. Better recordkeeping of medication use, efficacy and side effects will be instituted and those records will provide evidence for or against this risk. If medications are found to be ineffective, research will be performed to determine if drug metabolism is affected by spaceflight. Studies to determine if spaceflight affects drug stability are currently underway.

II. Executive Summary

Limited information on medications used in space clearly demonstrates a deviation from standard clinical practice on Earth both in terms of therapeutic dose and regimen. Also, polypharmacy (i.e., the treatment of one indication with multiple medications all of which are intended to treat the same clinical condition) in space has been reported by astronauts and flight surgeons indicative by the use of multiple doses of the same medication and/or concomitant use of medications with similar pharmacologic action. These observations coupled with the knowledge that therapeutic effectiveness of drugs can be affected by physical-chemical changes of the formulation resulting from stability and shelf-life alterations, extreme environmental challenges aboard the spacecraft, and/or by changes in the pharmacokinetic/pharmacodynamic profile of a drug caused by physiological adjustments in a microgravity environment imply that **therapeutic effectiveness of drugs in space may be different than on Earth**.

Storage of medications on lunar and martian missions will be outside the protective magnetosphere of the Earth and, therefore, may be susceptible to unique environmental factors including heavy ion radiation that may affect drug stability. Distance and feasibility of real-time communication may also play a role in effective clinical practice in space. Additionally, drug absorption and bioavailability, distribution and metabolism, and elimination of medications may be altered in partial gravity environments resulting in reduced efficacy or altered therapeutic profile of drugs in space. In the ensuing discussion we present evidence from astronaut medical records and research results from spaceflight and ground analog studies to illustrate the following gaps and associated risks:

a) Absence of records and documentation of unusual medication use practices that can precipitate drug-drug and drug-physiology interactions that can lead to unexpected and dangerous clinical outcome;

b) Unavailability of reliable data on pharmacokinetics, bioavailability and pharmacodynamics of medical kit components, especially those with a narrow therapeutic window, resulting from altered gastrointestinal, hepatic and renal function, which in turn can affect treatment efficacy;

c) Inadequate information on drug stability and shelf-life in a radiation-rich environment; and

d) Uncertainty of optimal treatment regimens for neurosensory disturbances, bone and muscle decrements and immunology and infection mitigation.

In the following discussion, we will also examine pharmaceutical and clinical literature as supporting evidence for risk of treatment failure in space. Finally, we will attempt to identify

knowledge gaps that must be addressed to mitigate the risk of treatment failure of acute and chronic illnesses during space exploration missions.

III. Introduction

Medications have been used in the NASA human spaceflight program since its inception to treat illnesses of a wide range of acuity. The list of medications in the spaceflight formulary has increased from a few medications for motion sickness in the early manned spaceflight program to a much larger and diverse set of drugs to treat illness and injury during current spaceflights. Medications for the treatment of common colds, aches, pains, insomnia, and other low acuity illnesses are standard in the current spaceflight formulary. Also included are neuro-cognitive medications, antibiotics, and medications to manage emergent medical situations like physical injury and cardiovascular crises. In addition to the standard care medications in the Space Shuttle and International Space Station (ISS) medical kits, astronauts are allowed to carry personal prescriptions in their personal packs for symptomatic relief of certain discomforts during spaceflight.

Transport and stowage of supplies during spaceflight, including medications, must fulfill certain engineering and safety requirements to prevent damage to equipment, prevent offgassing, and allow for easy access and use by crewmembers. To fulfill these requirements, engineers repackage drugs—under the supervision of flight surgeons—into zip lock bags and plastic amber vials which are stored in Velcro closure fabric boxes. Medications are inventoried with "part numbers" in engineering documents. This configuration of packing, stowage, and tracking is used currently on the Space Shuttle and ISS.

In most clinical settings where medications are dispensed to provide medical care to patients, the institution maintains an approved list of drugs for treatment called a "formulary;" this formulary is chosen, often by an expert committee of medical and institutional professionals, taking into consideration a number of criteria such as cost, efficacy, safety and product availability, to name a few. Similarly, a special Formulary Committee convened by the NASA flight medicine office periodically reviews the Space Shuttle and ISS formulary and makes recommendations based on the above mentioned criteria. Medications from the space program's international partners may be chosen by similar methods. For example, Russian and other international crewmembers use medications that are not approved by the U.S. Food and Drug Administration (FDA), but they are approved by similar agencies in their home countries. As such, a flight-specific drug information monograph that includes medications from all participating international partners is maintained and made available to crewmembers, flight surgeons, and other clinicians and scientists.

NASA is currently preparing for a transition from ISS and Space Shuttle operations to the Crew Exploration Vehicle (CEV), lunar outposts, and extended-duration missions to Mars. As a part of this transition, the Space Life Sciences Directorate is reviewing procedures and processes related to medical operations and crew health. The goal of this effort is to identify medical risks and associated knowledge gaps for providing safe passage to extraterrestrial missions by astronauts. Future missions, characterized by longer duration and larger crew compliment, coupled with extremes of environmental factors and distance, are likely to present emergency medical incidents that require remote and extended therapeutic intervention capabilities. Here, we present existing evidence related to the risk of treatment failure due to ineffective medications in space.

IV. Evidence

A number of physical, physiological, and environmental factors unique to spaceflight are suspected to affect therapeutic outcome. These factors include, but are not limited to: a) high demand activity schedules, b) sleep and circadian disturbances, c) physical constraints of living conditions, d) nutritional changes, e) pharmacokinetic and pharmacodynamic changes resulting from physiological and biochemical responses to the altered gravity environment, f) polypharmacy practices leading to drug interactions, and g) other flight-specific requirements such as extravehicular activities (EVAs). In addition, environmental factors unique to spaceflight may also affect stability of pharmaceuticals in space, which can influence bioavailability and therapeutic index.

A. Space Formulary and Drug Information Data Base

A brief history of drug use in the manned spaceflight program is useful to understand before discussing drug usage patterns and tracking efficacy. Medications have been used in NASA's manned spaceflight program since its inception. The first four Mercury flights carried four medications, cyclizine (45 mg in a 0.9-ml injector, for motion sickness), meperidine hydrochloride (90 mg in a 0.9-ml injector, for pain), epinephrine (1:1000), and dextroamphetamine. On the fifth Mercury flight, only injectable cyclizine and meperidine were flown; on the sixth and last Mercury mission, these drugs were supplemented with dextroamphetamine tablets, provided both in the suit and in the survival kit. On this flight, pilot Gordon Cooper became the first astronaut to take oral medication during spaceflight, taking dextroamphetamine before starting the retro sequence (NASA, 1967).

The medication kit was expanded considerably for the Gemini program. Crewmembers were asked to test each of the medications in the kit before flight to judge their individual reactions to them. The recommendation of the flight physicians at the time was to take dextroamphetamine sulfate with a decongestant before the reentry sequence. Antimotion-sickness medication was also taken in one instance before atmospheric reentry to reduce the possibility of motion sickness after the spacecraft splashed down. Because most of the Gemini flights were fairly brief, Lomotil (diphenoxylate)—an inhibitor of gastrointestinal motility—was prescribed to assist in avoiding defecation during flight (Cunningham, 1977). At the time of the Gemini summary conference in 1967, the consensus was that no difficulty had been experienced in the use of oral medications, which in the opinion of the flight physicians had produced the desired effects.

For Apollo missions, medications were provided in two separate kits, one located in the command module and one in the lunar module. Two cardiovascular drugs, quinidine sulfate and dipyridamole, were added to the basic Apollo kit for the Apollo-Soyuz Test Project (Bartelloni et al, 1975). According to Hawkins and Ziegleschmid (1975), the medications taken most frequently during the 10 Apollo flights were aspirin, acetaminophen, Actifed (triprolidine), Seconal (secobarbital), Lomotil, Afrin (oxymetazoline), and Marezine (cyclizine), all of which, except for the nasal spray Afrin, were in tablet form and taken orally.

Medications carried on Space Shuttle missions have varied somewhat from flight to flight, depending on the individual needs of the crewmembers. Medication use during Space Shuttle flights seems to be more prevalent than during earlier programs, perhaps because drugs are now

provided in easy-to-use forms, more medications are available in the formulary, and the incidence of ailments during spaceflight is more prevalent due to increased mission duration. Generally, standard formulary for the Space Shuttle and ISS flights include the following list (among others):

> Acetazolamide, Albuterol, Amikacin, Amoxicillin/clavulanate, Atropine, Azithromycin, Bisacodyl, Bupivacaine, Cefadroxil, Ciprofloxacin, Cyclopentolate, Dexamethasone, Dextroamphetamine, Diazepam, Diphenhydramine, Epinephrine, Fentanyl patch, Fluconazole, Guaifenesin, Guaifenesin/Pseudoephedrine, Haloperidol, Imipenem, Lidocaine, Loperamide, Loratidine, Lotrimin cream, Meperidine, Metronidazole, Morphine, Mupirocin, Mylanta, Naloxone, Nitroglycerin, Norgestrel/Ethinyl Estradiol, Pepto-Bismol, Prednisone, Promethazine, Propanolol, Pyridium, Silver Sulfadiazine Cream, Silver Nitrate, Trimethoprim/Sulfmethoxazole, Tobramycin/dexamethazone ophthalmic, Valcyclovir, Verapamil, Vicodin, Trifluridine ophthalmic

The majority of medications taken to date have been ingested by mouth in tablet form although intramuscular injections, rectal suppositories, ocular preparations, and topical agents are also available in the onboard formulary. **The relatively extensive formulary currently manifested on the Space Shuttle and ISS flights, while providing assurance for adequate treatment capabilities in space, increases the risk of treatment failure and/or dangerous drug interactions owing to the gap on the pharmacokinetic/pharmacodynamic behavior of the candidate drugs in space and resultant clinical outcome.**

There is limited evidence in the literature of reduced efficacy of some drugs during spaceflight (Vernikos, 1995; Cintrón & Putcha, 1996). Additional evidence comes from verbal reports from physicians and astronauts, postflight medical debriefs database, and results from Detailed Supplemental Objective (DSO) research protocols. A more systematic evaluation of medication use trends during spaceflights has only recently been initiated at NASA.

The astronaut medical database consists of astronaut longitudinal medical records, that is, flight surgeon reports from personal medical conferences during flight and postflight medical debriefs. This database of medication use is different from databases used in standard hospital and clinical care institutions for several reasons. Unlike hospitals and large clinical facilities in which medication use is tracked by simultaneous, real-time tracking systems (physician orders, physician notes, pharmacist prescription tracking systems, medication administration records, and nursing notes, all of which are used for medical quality assurance and quality control and to prevent mishap or mistreatment and promote prompt intervention when needed), medication use tracking during spaceflight is neither real-time nor has the luxury of any redundancy. Instead, medication use is communicated via secure radio channels between flight crews and ground-based flight surgeons according to a planned but limited schedule. Busy schedules limit on-console communications between astronaut crewmembers and flight surgeons to approximately once a day depending on the mission configuration. In addition, the on-console communication loop at times only involves the flight surgeon and the mission commander. Furthermore, because of limited space and close quarters, the confidentiality of medical information during missions may be an issue for some astronauts, limiting open communication of medication use with the flight surgeon. To provide redundancy, astronauts participate in a medical debrief once upon landing, and again several days later. During these medical debriefs, crewmembers relate drug usage information. In addition, inventory practices for drugs flown during spaceflight have not been ideal. Inventory of medications returned from spaceflight indicates that at least on some

occasions, the number of drugs returned from spaceflight does not match the reported drug consumption in space. On other occasions, such as when the Space Shuttle fleet is grounded and transport to the ISS is managed by the Russian Soyuz vehicles, drugs flown in space have not been returned to the ground for inventory due to mass and space limitations in the Soyuz, but instead were ejected to burn up upon atmospheric reentry; thus, the use of an inventory to track medication use for such missions is not possible. Therefore, an important gap related to the risk of ineffective medications is the tracking of medication use, efficacy, and real-time monitoring of therapeutic outcome in space.

Review of crew medical debriefs showed that promethazine (PMZ) was less likely to produce sedation in flight than when used on the ground (Bagian & Ward, 1994) indicating that either reduced potency or altered bioavailability, pharmacokinetics, and pharmacodynamics brought about by physiological changes in space, or both. Both physicians and astronauts report use of higher and more frequent doses of medications for sleep and for the treatment of space motion sickness (SMS) on several Space Shuttle flights compared to what would be expected on the ground. One such example is the use of a promethazine dose several times higher than normal dose during spaceflight to achieve treatment efficacy with no increase in side effects reported (Clark, 2005). Other unusual treatments are dispensing a combination of scopolamine and dextroamphetamine tablets in a capsule for single dose administration and administration of midodrine and promethazine in sequence at landing. **All of these unusual medication use practices have the potential to result in dangerous and untoward clinical outcome.**

Analysis of medication use and efficacy records compiled from postflight medical debrief documentation for Space Shuttle flights, STS-1 through STS-80 (Putcha et al, 1999) showed that, of the 219 logs (person-flights) examined, 94% recorded taking some medications during the mission. Most of the doses were taken orally (87.8%); 4.8% were taken intranasally, 4.3% intramuscularly, and 2.1% rectally. Less than 1% of the doses were by topical application or intravenous injections. Of those who have taken medications during flight, 47% took SMS formulations, 44.7% used sleep aids, and a lesser percentage took analgesics or anti-inflammatory drugs (Figure 21-1).

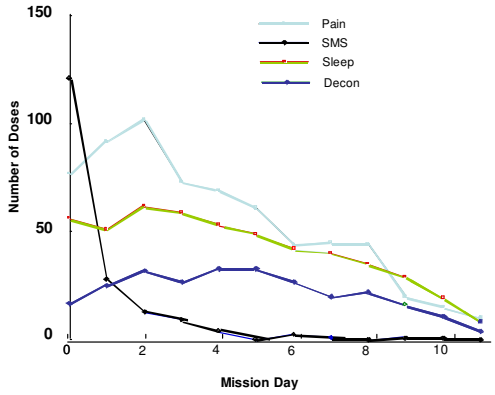

Figure 21-1. Medication use profiles from STS-1 through STS-80.

An ongoing analysis of an extended dataset covering more Space Shuttle missions, STS-1 through STS-94, showed similar trends with pain medications accounting for approximately 37% of all prescriptions recorded, followed by sleep (22%), SMS (18%), decongestion (14%), and all others (14%) as shown in Figure 21-2.

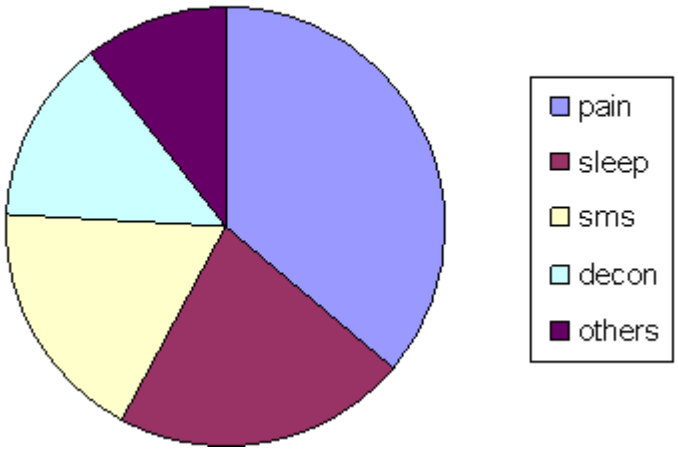

Figure 21-2. Percentage of prescriptions by indication recorded on STS-1 through STS-94.

Another observation of significant importance from these medical debrief records is the prevalence of a trend of polypharmacy during flight. Polypharmacy, in clinical settings, refers to treatment with multiple medications at the same time; sometimes, polypharmacy also means the use of multiple medications to treat the same indication at the same time (Kingsbury et al, 2001; Nananda, 2005; Salazar et al, 2007). Other definitions of polypharmacy have been used in the literature and sometimes include the use of unnecessary or irrational choices of medications (Salazar et al, 2007). Polypharmacy is a concern in health care on Earth because in the populations it is most common, such as the elderly and those with chronic illness, the practice presents an increased risk of comorbidity (Covington, 2006; Salazar et al, 2007).

There is a body of evidence on risk assessment and analysis of polypharmacy of insomnia mainly in the elderly and dialysis patients, but low subject numbers and the lack of well-designed or properly tracked studies limit conclusions about appropriate treatments (Novak et al, 2006; Veehof et al, 2000). **Similarly, the small number of astronaut reports, insufficient information, and confidentiality issues preclude the ability of risk assessment and assurance of effectiveness of multiple treatments administered in space for enhancing restful sleep.** Some of the confounding factors that can modify treatment outcomes with sedative hypnotics in space include stressful and heavy workload schedule, suboptimal sleeping conditions, noise, air quality and circadian disturbances. Antihistamines (including promethazine), benzodiazepines, and other sleep aids (non-benzodiazepine GABA agonists, melatonin, melatonin receptor agonists, etc.) are often used by astronauts. The medication use database also indicates incidents of polypharmacy with sleep medications (for example, benzodiazepines taken with an antihistamine, concomitant use of more than one benzodiazepine, more than normal dose and regimen of anti-motionsickness and/or sleep medications). The use of multiple sleep medications probably stems from an ineffectiveness perceived by astronauts of the medication used. Other instances of polypharmacy exist, but for the most part, these instances relate to the use of multiple medications to treat multiple symptoms at the same time such as for

SMS, sleep, pain, and congestion, concomitantly. **All of these practices of medication use in space can result in dangerous and adverse treatment outcomes.**

It has been suggested in a recent report that acute urinary retention (AUR) reported during spaceflight may be a result of polypharmacy practice of SMS medications (Stepaniak et al, 2007). Motion sickness medications generally exert their effects via anticholinergic activity, a side effect of which can be urinary retention. Combining medications can result in drug-drug interaction—in this case, the combination of scopolamine and promethazine, each of which can cause urinary retention as a side effect, may have resulted in an additive pharmacodynamic drug-drug interaction which resulted in profound acute urinary retention. AUR is a medication side effect that can be transiently incapacitating, but can also cause further comorbidity by increasing the risk of urinary tract infections from increased catheterization, and increasing renal stone formation, due to reduced urine flow.

Certain drugs can influence the formation of urinary stones by affecting urine formation or by directly affecting biological handling of stone forming chemicals (Marangella, 2005; Bihl & Meyers, 2001). Medications can cause urinary retention in a variety of ways, such as by a variety of biochemical and physiological factors. Other medications cause or influence urolithogenesis by altering blood and urine pH, by increasing the production of a stone forming chemical from other physiological processes, and by reducing the excretion of stone-forming chemicals from the renal tubules. Among the combined spaceflight formulary, medications that are known to be common stone formers are the loop diuretics, acetazolamide, laxatives, ciprofloxacin, sulfa medications, triamterene, guaifenesin, and ephedrine.

Other medications contribute to stone formation because their own metabolites are stone forming chemicals. Oxalate and urate are both constituents of several renal stone types; they are also metabolites of many drugs and foods (or present in the latter) and therefore can contribute to renal stone formation. In the context of space missions, the effects of drugs on the formation of renal stones may be further exacerbated in conditions of reduced vascular volume and body water, both of which have been reported (Borghi et al, 1993).

This un-counseled polypharmacy trend of medication use in space described above could result in dangerous clinical outcomes. For example, there are several drugs in the in-flight formulary that have similar metabolic pathways. One example of a potential drug-drug interaction has been identified as relevant only to NASA, but not the general public. Recently, the peripheral alpha-adrenergic agonist midodrine was evaluated as a countermeasure for postflight orthostatic intolerance. Crewmembers who routinely take Phenergan as a postflight antiemetic volunteered to participate in the evaluation. Results from a ground-based analog study to examine possible interaction between promethazine and midodrine, a relatively new drug, indicated that 7of 10 normal subjects who were given midodrine followed by promethazine experienced mild to moderate akathesia (aggression, anxiety, malaise, dysphoria), potentially due to higher circulating concentrations of promethazine resulting from competitive inhibition at the site of metabolism of promethazine. This presents a classic case of cytochrome 2D6 metabolic drug interaction causing dangerous side effects with concomitant treatment (Platts et al, 2006). There could be serious consequences had these two drugs been taken during landing (one for orthostatic hypotension, one as an antiemetic). Changing the order of administration of the two drugs—promethazine given before midodrine—could result in higher blood levels of midodrine leading to the possibility of a hypertensive episode in astronauts. Fourteen drugs in the current formularies for Space Shuttle and ISS have major metabolic pathway by cytochrome 2D6, which can present the potential for similar drug interactions. Additionally, this enzyme is significantly

inhibited by nine other medications in the flight formularies. **These limited results with two drugs, coupled with the extensive on-board formulary and polypharmacy practice in space, presents a serious gap of knowledge on clinically significant drug interactions that can potentiate or inhibit pharmacological activity of candidate drugs in the formulary. All operationally relevant drug interactions must be identified carefully, both by literature review and by conducting specific drug interactions research, to assure safe and effective treatment for astronauts on future missions.**

In concurrence with the debrief database analysis, medication use logs from 10 astronauts who participated in a research protocol with promethazine, "Detailed Science/Supplementary Objective 490: Bioavailability and performance effects of promethazine during spaceflight" (DSO 490), were also analyzed. Data collected so far from this DSO indicate that as many as 80% of the astronauts participating in this study used either sleep aids (including promethazine, which has potent sedating properties) during flight. The percentage of astronauts taking sleep medications increased throughout the first several days of flight and remained high through the remainder of spaceflight (Figure 21-3). But use of sleep medications did not influence sleep duration, which remained at approximately 80-85% of that on the ground. Nine of the 10 astronauts who participated in this study took sleep medications. Of these, two participants took more than one sleep medication at the same time at least once during spaceflight. Use of multiple sleep medications occurred on flight days (FD) 3, 4, 6, and 7. In addition to the factors described earlier that may modify therapeutic effectiveness of sleep medications during spaceflight, factors related to the formulation itself such as reduced drug stability due to sub-optimal stowage conditions during flight, and changes in bioavailability and pharmacodynamics of drugs during flight may also adversely affect drug effectiveness in space. Use of other drugs such as caffeine, dextroamphetamine, and decongestants, could also contribute towards a reduction in effectiveness of promethazine on sleep quality and efficiency. While equivocal in regards to the reduced effects of promethazine on sleep, these results clearly indicate polypharmacy practices in space.

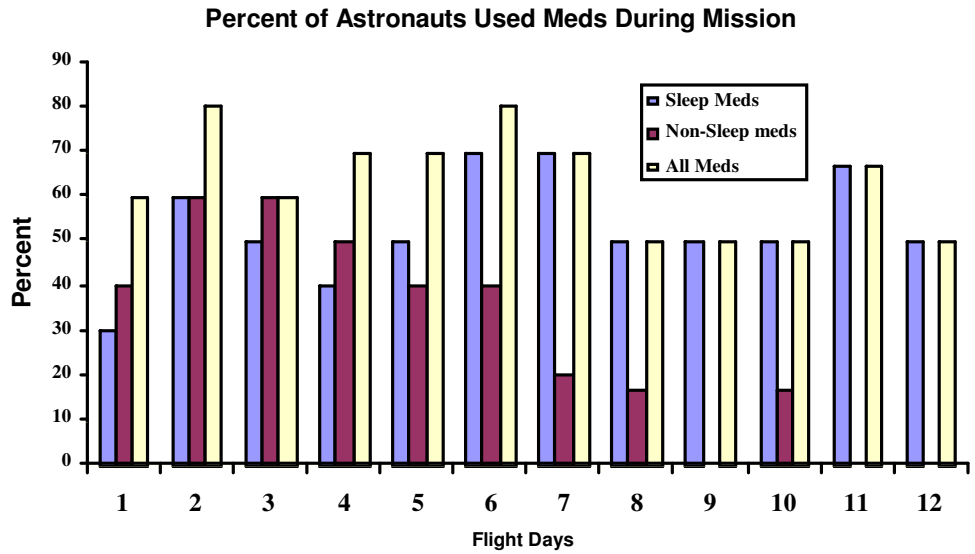

Figure 21-3. Sleep medication use in DSO 490: Bioavailability and performance effects of promethazine during spaceflight. Percent of astronauts in the study (n=10) who used sleep aids compared with non-sleep aids and all other medications.

B. Clinical research during spaceflight

Therapeutic effectiveness is a function of pharmacokinetics and pharmacodynamics of administered drug. Pharmacokinetics (PK) is the mathematical description of the processes that control drug concentrations in the body; these processes are absorption, distribution, metabolism, and elimination of a drug after administration, often by mouth (Gibaldi & Perrier, 1982). Alteration in any one of these four processes can affect a drug's efficacy or safety profile (Putcha & Cintrón, 1991; Graebe et al, 2004; Lane et al, 1993; Tietze & Putcha, 1994). Pharmacodynamics (PD) is the mathematical description of the effect elicited by the drug, both therapeutic as well as toxic; pharmacodynamic effects are always dependent on a drug's pharmacokinetics. Therapeutic efficacy of a drug, therefore, is a function of PK/PD profile of the drug and the interrelationship of physiological factors that influence PK/PD.

A number of physiological factors that affect absorption, distribution, metabolism and elimination of drugs may be altered during spaceflight suggesting strongly that PK/PD profiles of drugs may be different in space from those on Earth (Derendorf, 1994; Saivin et al, 1997; Lathers et al, 1989).

The absence of a gravity vector combined with changes in body posture, fluid loss, and fluid redistribution during spaceflight, decreases the rate of gastrointestinal motility (Grigoriev et al, 1996). Furthermore, changes in blood flow patterns resulting from exposure to microgravity decrease the rate of gastric emptying (McClean et al, 1978), which depresses the hunger sensation (Nicholl et al, 1985). Russian studies of rats and humans suggest that gastric hypersecretion takes place during simulated and actual weightlessness. Simultaneous increases in human gastric and pancreatic secretions were reported after 140- and 175-day flights on Salyut-6; however, after an 185-day flight that included the use of countermeasures, these increases were described as less distinct (Smirnov, 1986). Changes in the gastrointestinal function can also adversely affect the bioavailability of oral medications and other ingested compounds (Winne, 1980; Woodmansey et al, 1983).

In a very early study on pharmacokinetics in space, owing to the technical difficulties associate with blood sampling and storage during spaceflights, saliva concentrations were used to assess pharmacokinetics of acetaminophen tablets (650 mg) in 12 crewmembers before and during 7 short-duration Space Shuttle flights (Cintrón et al, 1987a). Saliva concentration time profiles of the drug were more variable during flight than during the preflight control period, with the most pronounced changes in absorption parameters rather than distribution or elimination parameters (Figure 21-4A & 21-4B).

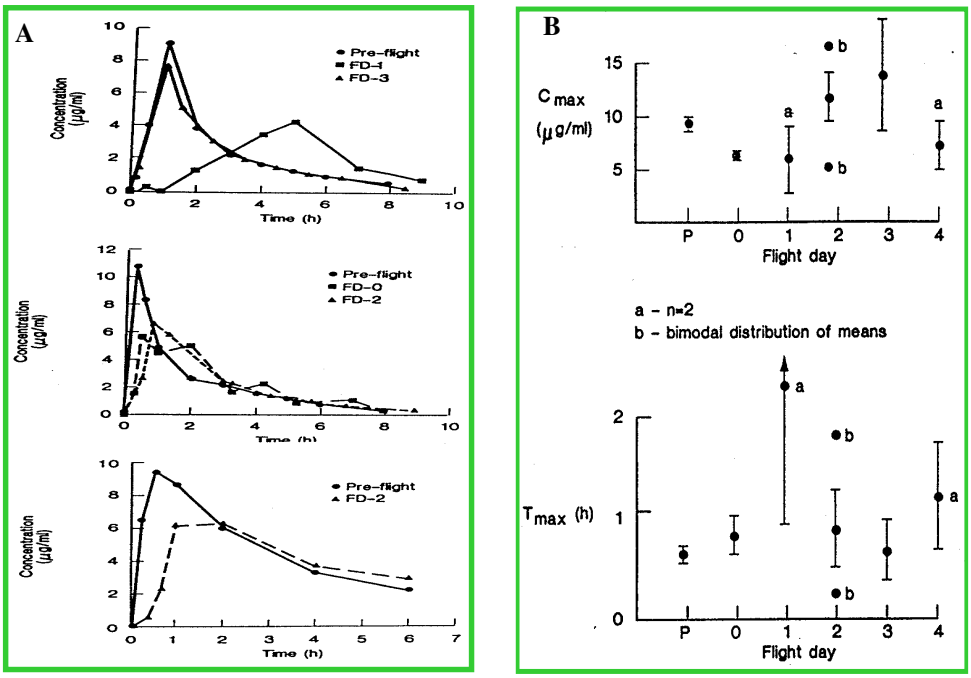

Figure 21-4. Saliva Concentration – Time profiles (A) and select pharmacokinetic parameters (B) of acetaminophen in astronauts.

Results from this preliminary investigation indicate that saliva concentration - time profiles of the drug during spaceflight are variable and different from those on ground, and absorption and bioavailability after oral administration are less than that on ground. A number of confounding factors such as motion sickness, changes in saliva-to-plasma ratio of acetaminophen in space, concomitant administration of motion sickness and sleep medications taken during an experimental flight day make it difficult to determine the rate and extent of changes in the pharmacokinetics of acetaminophen from these limited data from spaceflight.

Subsequently, an investigation to examine gastrointestinal motility using noninvasive lactulose breath hydrogen test was conducted on an extended duration flight with two crewmembers. Crewmembers ingested a 20 g dose of lactulose and a liquid oral dosage of acetaminophen (syrup, 650 mg) after a light breakfast and collected breath and saliva samples at regular time intervals before, three times during and after space flight; breath samples were analyzed for hydrogen levels and saliva samples were analyzed for acetaminophen concentrations. Gastrointestinal transit time (GITT) was estimated from breath hydrogen profiles and maximum concentration (Cmax) and area under concentration versus time curve (AUC) were calculated from saliva concentration profiles. Results indicated that GITT increased more than 30% in both subjects on all flight days and remained elevated postflight (Figure 21-5). C_{max} and AUC were both dramatically reduced later in flight by 35 and 39% compared to their preflight values (Boyd et al, 2005a). The concomitant decrease in both values indicates significant reduction in oral bioavailability of acetaminophen during spaceflight. As can be seen, the documented reduction in GI motility can prolong residence time of ingested medications in the GI tract that can negatively influence bioavailability of many orally administered medications.

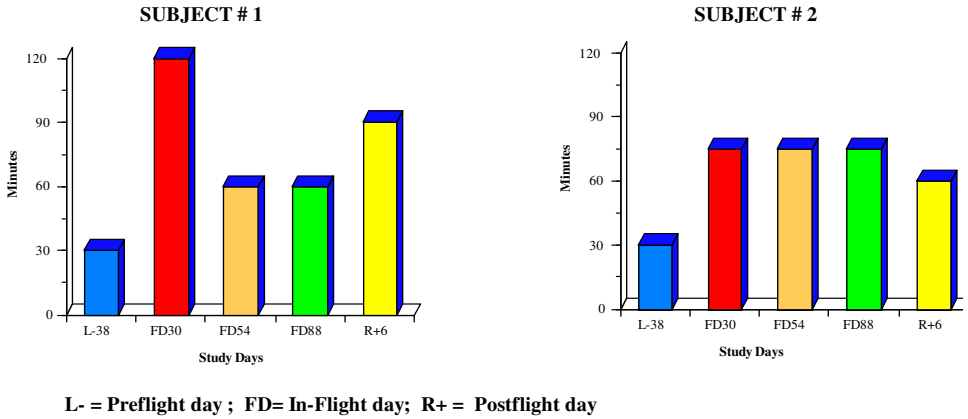

Figure 21-5. Gastrointestinal transit time during long duration spaceflight.

It should, however, be noted when salivary concentrations are used for estimating pharmacokinetics, the potential exists for confusing results due to residual concentrations of the drug in saliva after ingestion as well as biochemical factors that can affect distribution of the drug into saliva, both of which can affect C_{max} and AUC estimates. Another factor that might influence drug levels in the central compartment (blood) is concomitant administration of other medications that might affect distribution and metabolism of acetaminophen. Results presented here also illustrate the lack of adequate experimental control of confounding factors such as frequent use of hypnotics/sedatives, atypical and non-uniform dosing and regimens and concomitant and frequent administration of medications in higher than standard dose and frequency.

C. Promethazine during spaceflight

Promethazine is an antihistaminic drug used on the ground as a decongestant, cough suppressant and antiemetic. During spaceflight, it is frequently used by astronauts for the treatment of SMS and to promote sleep.

Data to date suggest that pharmacotherapeutics may be different in space due to changes in gastrointestinal motility and organ function of the liver and kidney which can affect pharmacokinetics, bioavailability and pharmacodynamics of drugs in space, and oral drug treatment may be ineffective or less effective in space. Additionally, chronobiological differences of spaceflight such as hormone levels, sleep patterns and suboptimal light conditions could also influence therapeutic outcome of certain neurosensory drugs. **A gap, therefore, is the lack of information on pharmacokinetics of operational medications for estimating risk of drug ineffectiveness and identifying mitigation strategies.**

D. Physiological studies during spaceflight

Several other physiological variables besides gastrointestinal function that can affect drug pharmacokinetics have been shown to be altered during spaceflight. Blood protein content, regional blood flow, and vascular volume among others, are altered during spaceflight. Changes in these parameters can affect drug pharmacokinetics and, thus, drug effectiveness.

Leach (et al, 1996) showed an increase in glomerular filtration rate, in nine astronauts on Spacelab Life Sciences (SLS) missions 1 and 2, without a concomitant increase in effective renal plasma flow. Glomerular filtration rate was increased on Flight Day (FD)1/2 and FD8 when compared to the corresponding preflight values in astronauts. The increase in glomerular filtration rate on early flight days is the result of fluid shedding to reduce misperceived hypervolemia. During short-duration spaceflight, it is known that glomerular filtration rate increases during FD1 and FD2. Later in flight, renal plasma flow decreases resulting in a decrease in glomerular filtration rate (Leach et al, 1991a, b).

Alterations in body fluid composition were also reported with concomitant reduction in overall plasma volume, interstitial fluid, cardiac output (Diedrich et al, 2007; Shi et al, 2004), and orthostatic intolerance upon return to Earth is one clinical syndrome resulting from these in-flight adjustments. Plasma volume, vascular volume, and total body water are all important physiological factors that influence volume of distribution of most drugs. A significant reduction in one or more of these factors can significantly increase blood concentration of drugs there by increasing propensity for side effects.

Additionally, blood albumin levels were shown to be altered during spaceflight (Guseva & Tashpulatov, 1979, 1980). Alpha-1 acid glycoprotein also has been shown to be decreased (but not in a statistically significant fashion) during spaceflight (Fisher & Gill, 1972); albumin and alpha-1 acid glycoprotein are both major drug binding proteins in blood, non-specifically binding acids and bases, respectively. Pharmacological effect of a drug is a function of the free or unbound systemic drug concentration; thus, alterations in the protein concentration that a drug binds to in the blood can, therefore, alter circulating blood levels of free drug thereby affecting it's therapeutic index.

E. Ground-based analog studies

Microgravity simulations such as horizontal and head down tilt bed rest are used frequently to develop and validate methods for use during spaceflight, to establish reference ranges of physiological parameters under well-controlled experimental conditions, and to accumulate data for identifying changes in drug dynamics and mechanisms of action.

In an earlier study conducted at the Johnson Space Center, the pharmacokinetics of orally and intravenously administered scopolamine were evaluated after 24 hours of anti-orthostatic bed rest. Plasma concentration profiles after oral administration (Figure 21-6A) indicated a significant decrease in the absorption and bioavailability of oral scopolamine; distribution and elimination of intravenous scopolamine were no different during bed rest than during ambulation. A similar trend indicating a reduction in absorption and bioavailability of oral scopolamine was also noted in an astronaut during spaceflight (Figure 21-6B).

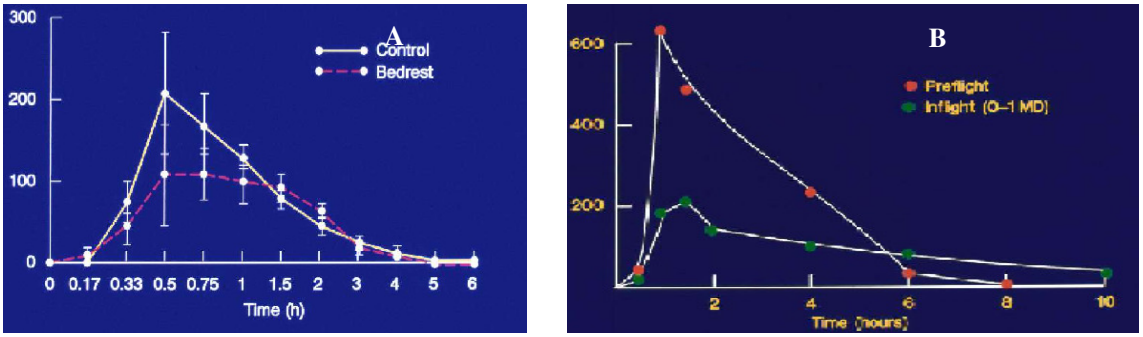

Figure 21-6. Saliva concentration; time profiles of scopolamine after oral administration of scopolamine (0.4 mg) during head down tilt bed rest (A) and spaceflight (B).

These early results suggest that the absorption of scopolamine, but not its distribution or elimination, may be affected during spaceflight and -6° head down tilt bed rest can serve as an effective ground-based analog for pharmacokinetic studies.

Since conventional research in space is difficult if not impossible due to technical constraints, time and distance factor and crew time limitations, a number of ground-based analogs such as head down tilt bed rest, dry and water immersion have been used as surrogates for a microgravity environment. Animal models like the tail suspended rat model were also employed in ground-based space physiology studies.

F. Gastrointestinal physiology and therapeutics with oral medications

Gastrointestinal function has been reported to be altered during spaceflight. Proteolytic enzymes have been shown to be activated as well as a redistribution of lipolytic activity in the gastrointestinal organs (Smirnov, 1986). Postflight reductions in glycoproteins of the submaxillary glands, gastric mucosa, and goblet cells of the small and large intestine have been shown in rats (Groza et al, 1983). Gastric emptying is suspected to be slower and more variable in microgravity due in part to a shift in the relationship between gravitational forces and viscous forces which interact to affect gastric emptying and gastrointestinal transit time (Amidon et al, 1991). Data in astronauts to date support the hypothesis that gastrointestinal absorption is altered for at least some of the drugs used in space. The reduced status of Vitamin D in astronauts on return from long-term missions on the ISS may indicate, among other things, a reduction in oral absorption of Vitamin D (Smith et al, 2005). Malabsorption is the inability of the gastrointestinal tract to absorb vitamins, nutrients, drugs, and any substance needed to maintain good health (Meyer et al, 1986; Meyer et al, 1988). In ground-based clinical practice, malabsorption is caused by disorders of metabolism, infections in the gastrointestinal tract, or anatomical features such as obstruction or surgery. Reductions in gastrointestinal motility during spaceflight caused by reduced gravity may induce a state of malabsorption during spaceflight.

1. Gastrointestinal motility and function

A number of clinical methods are available for determining gastrointestinal patho-physiology. Acetaminophen is the quintessential pharmacological marker for measuring gastric emptying noninvasively (Toes et al, 2005; Sanaka et al, 1998). Acetaminophen is generally

regarded as safe and well tolerated when used in the recommended dosage range and frequency. It is not absorbed in the stomach but is rapidly and almost completely absorbed from the upper gastrointestinal tract making it an indicator for reductions in gastric motility, which can increase gastric emptying time. The use of nondrugs as surrogates for drug absorption (such as scintigraphy) as noted by Willems (et al, 2001) is inherently less informative, especially when whole organismal pharmacokinetic studies can be used with well tolerated drugs which are frequently used during space missions and are in themselves excellent markers for gastric emptying and drug absorption. While scintigraphy is an accurate and detailed method to study the phenomenon of gastric emptying, its value as a predictive measure for drug absorption is less accurate than the absorption of a pharmaceutical, like acetaminophen.

Another important determinant of gastrointestinal motility and function is intestinal transit of orally administered substances (Holgate & Read, 1983; Hunt & Spurell, 1951; Levine, 1970). Motility and function can be estimated indirectly by noninvasive breath hydrogen test after lactulose ingestion (Bond & Levitt, 1972); lactulose breath hydrogen test was used both in head down tilt bed rest and in flight studies at NASA to estimate changes in gastrointestinal transit time. The lactose breath hydrogen test is commonly used for clinical diagnosis since it is inexpensive, noninvasive and easy to administer. Its limitations include accuracy, specificity and uncomfortable gastrointestinal side-effects (Riordan et al 1996; Santavirta 1991).

2. Gastrointestinal bacterial hyperproliferation and drug absorption

Reduction in gastrointestinal motility in bed ridden patients has been shown to cause bacterial proliferation in the intestine (Husebye, 2005); bacterial proliferation can affect drug absorption due to the high capacity of bacteria to metabolize drugs. The impact of gut flora on drug absorption is well known (Martinez & Amidon, 2002). Depending on the physiochemical properties of the drug, nutrient, or xenobiotic in question, gut flora can reduce absorption (Davis et al, 1972), increase absorption (Aldercrutz et al, 1984), or alter enterohepatic recycling of drugs (Ilet et al, 1990).

Human intestinal microecology has been reported to be dysbacteriotic during spaceflight (Smirnov, 1987). No literature exists on the effects of prolonged bed rest or microgravity on nonspecific proliferation of gastric bacteria or *H. pylori*. *H. pylori* can significantly affect orally administered drug absorption by Pangastritis, a type of malabsorption involving both the atrophy of the gastric body as well as atrophy of the antral mucosa, associated with *H. pylori* overgrowth (Varis et al, 1993; Karnes et al, 1991; Fukao et al, 1993; Carmel et al, 1994; Kuipers et al, 1995; Negrini et al 1996). *H. pylori* is commonly regarded as the major cause for nonspecific gastritis (Taylor & Blaser, 1991) and chronic atrophic gastritis (Fukao et al, 1993). Gastritis is known to interfere with the absorption of drugs (Welling, 1984); therefore, it is prudent to evaluate the risk of proliferation of *H. pylori* in relation to drug bioavailability as well as the risk it may pose to astronauts as a pathological species.

Both horizontal and head down tilt bed rest have been reported to induce many physiologic changes similar to those observed in space such as muscle atrophy, bone demineralization, redistribution of fluids, and decreases in plasma volume and red blood cell mass (Nicogossian et al,1979; Genin, 1977; Sandler, 1976; Sandler and Vernikos, 1986). Head down tilt appears to elicit some of the early physiological effects of microgravity more precisely than horizontal bed rest (Kakurin et al, 1976). In particular, head down tilt produces more rapid and pronounced fluid shifts and cardiovascular changes than horizontal bed rest (Blomqvist et al, 1980). As such, head

down tilt bed rest was used to evaluate noninvasive techniques for measuring gastrointestinal function involving the measurement of acetaminophen concentrations in saliva after an oral dose (650 mg) and measurement of hydrogen in the breath after lactulose administration (20 g; Putcha, 1991). Results from this study indicated that head down tilt induces changes in gastrointestinal (GI) motility. As shown in Figure 21-7, a greater than 40 percent increase in the gastrointestinal transit time was observed during a ten-day head down tilt bed rest study. Acetaminophen concentrations in plasma over time from this head down tilt study were analyzed to assess changes in the pharmacokinetics of the drug during bed rest. The half-life of gastric emptying time was much longer during the bed rest phase (mean=25.5 min) when compared to the ambulatory group (mean = 6.9 min) (Srini et al, 1994).

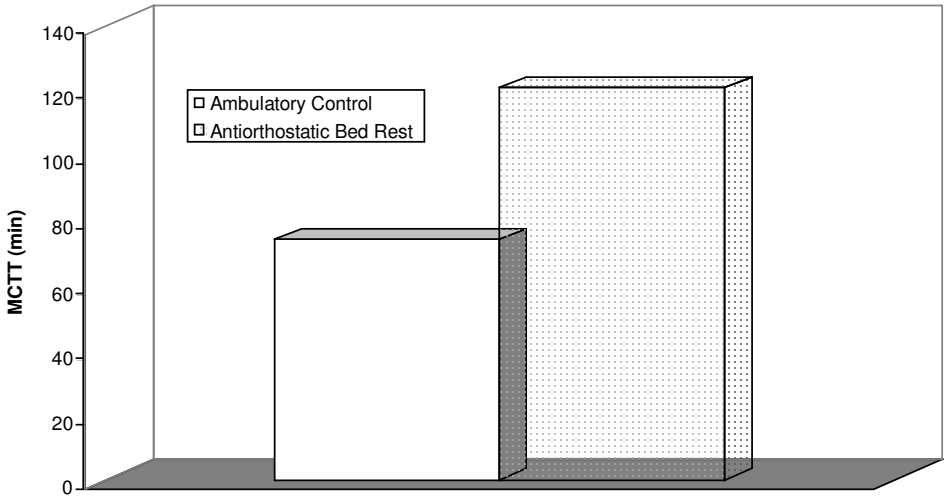

Figure 21-7. Gastrointestinal transit time of 20 grams of lactulose after 10 days of head down tilt bed rest.

Results from studies on gastrointestinal motility and drug absorption in space indicate a significant increase in gastrointestinal transit time during and after spaceflight (Putcha et al, 1996; Putcha and Cintrón 1991).

3. Pharmacokinetic models for pharmacotherapeutics

Pharmacokinetic and pharmacodynamic simulation models have been widely used by the pharmaceutical industry for optimizing clinical trials and by the U.S. FDA for evaluating therapeutic profiles of new drugs. Predictive PK/PD simulations are used in clinical trials because they improve the ability to evaluate and understand the consequence of various study designs (FDA, 1999a, b, c; Gobburu & Marroum, 2001) and are often used to predict treatment outcomes (Clermont et al, 2004; Yuan et al, 2004). Since in-flight research is limited by time and sample constraints, development of predictive models will allow optimization of sample and data collection during spaceflights. As such, using data collected with acetaminophen during head down tilt bed rest and during flight, a physiologically based pharmacokinetic model was constructed. The model suggests that the reduction in gastric emptying rate changes the pharmacokinetics of acetaminophen, as seen during head down tilt bed rest and during spaceflight (Figure 21-8, Srinivasan, et al, 1994). Similar models derived from robust data from

ground-based analog and limited in-flight experiments will assist in optimizing flight experimental design and predicting changes in PK/PD of clinical significance for drugs used in space.

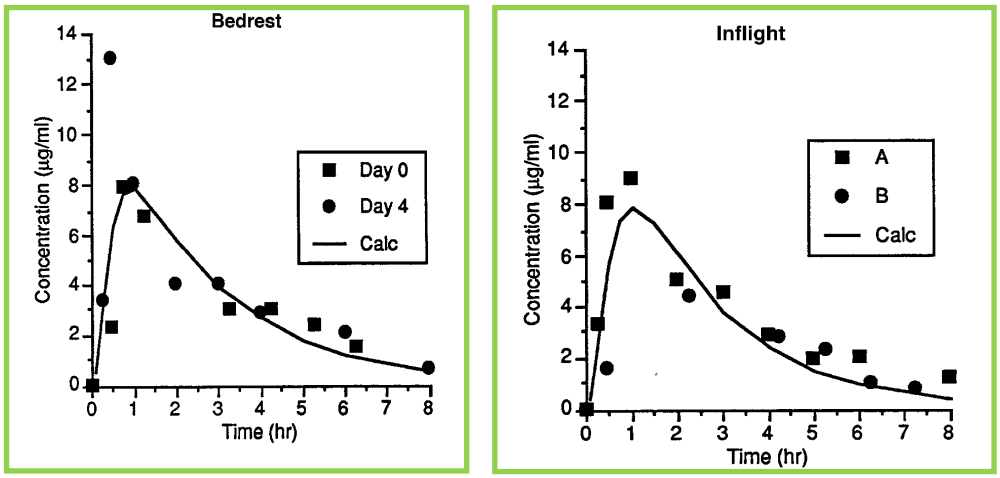

Figure 21-8. Predictive model acetaminophen with GI emptying changes.

4. Reduced bioavailability of oral medications during bed rest

Promethazine, the preferred anti-motionsickness medication, is available to astronauts as intramuscular injection, oral tablets, and rectal suppositories. All three forms have been used by astronauts during spaceflight. Studies (Gandia et al, 2003) have shown no change in the relative bioavailability of promethazine during head down tilt head down tilt when compared with normal ambulation but the study design may have inter-treatment variability.

5. Drug clearance in head down tilt bed rest

The term 'clearance' is integral to pharmacology and relates to the rate of disappearance of drug from blood; as such, clearance relates to the elimination of drug from the body (Gibaldi & Perrier, 1982). Increased clearance generally results in decreased total body exposure and often to decreased therapeutic effects; conversely, decreases in clearance can result in higher concentrations and exposure and lead to increased therapeutic and toxic effects. The kidney and liver are the major organs of clearance for most drugs and toxicants, although other organs such as the lungs can clear substance from the body as well. The clearance of drugs from an organ is the product of blood flow through the organ and the extraction ratio of the organ, a concept which accounts for metabolism in the organ. Total systemic clearance is the sum of all organ clearances. Head down tilt bed rest has been shown to affect both renal and hepatic clearance.

Renal clearance is expressed mathematically as the sum of glomerular filtration rate, active tubular secretion, and tubular reabsorption (Gibaldi & Perrier, 1982). Leach (et al, 1996) showed an increase in glomerular filtration rate in 9 astronauts on SLS-1 and SLS-2, without a concomitant increase in effective renal plasma flow (Leach et al, 1996). Glomerular filtration rate was increased on FD1/2 and FD8 when compared with values in the same astronaut preflight. The increase in glomerular filtration rate on early flight days is the result of fluid shedding to reduce misperceived hypervolemia. In short-term spaceflight, it is known that glomerular filtration rate increases during FD1 and FD2. Later in flight, renal plasma flow

decreases resulting in a decrease in glomerular filtration rate (Leach et al, 1991a, b). As nearly all drugs are cleared by renal excretion, and therefore depend on glomerular filtration rate for elimination from the body, the differential effects of spaceflight on renal clearance can affect pharmacokinetics of drugs in such a way that can alter therapeutic effectiveness of drugs in space.

Hepatic clearance is comprised of both elimination of compounds into the bile and enzyme mediated metabolism. Indocyanin green is eliminated solely by hepatic metabolism and has a very high hepatic extraction ratio; as such, its systemic clearance is equivalent to hepatic blood flow and is used as a marker for hepatic blood flow in relation to drug metabolism (Levy et al, 1967). In an early study with 10, healthy, non-smoking men, indocyanin green was administered intravenously during normal ambulation and following 24 hours of head down tilt, on separate occasions, and its clearance was compared between ambulation and head down tilt conditions. Hepatic blood flow was 43% less during head down tilt when compared to the value seen in normal ambulation. Furthermore, hematocrit was increased from 60 to 77% during head down tilt (Putcha et al, 1988). Each of these factors can independently affect the pharmacokinetics of drugs, and their specific effects are drug dependent. Reductions in hepatic blood flow during spaceflight can affect drugs which are cleared by the liver and effectively increase both the drug's half-life and AUC. For drugs with a direct relationship between pharmacokinetics and pharmacodynamics, this change can result in prolonged and/or exaggerated drug effect A higher than normal concentration in the blood as seen during head down tilt presents a potential increased intensity and resulting side effects. For drugs with less direct relationship, the decrease in hepatic blood flow may cause other untoward effects.

Another study demonstrated increased total body clearance of antipyrine after 3 days of bed rest (Elfstrom and Lindgren, 1978); increases in clearance of antipyrine indicate increased oxidative metabolism in the liver. Pharmacokinetics of other drugs, intravenous lidocaine and penicillin, however, were not changed after 7 days of horizontal bed rest (Kates et al, 1980).

Hepatic extraction ratio is a function of the intrinsic metabolizing capacity of the liver. Metabolism is frequently described in terms of oxidative metabolism, Phase I, and conjugative metabolism, Phase II. Both types of metabolism generally improve the water solubility of xenobiotics in order to increase the rate of excretion. Phase I metabolism enzymes, the cytochrome p-450 (CYP) group, have been shown in rats to be affected by microgravity analog, tail suspension (Lu et al, 2002). Hepatic cytochrome, CYP4A1, was found to be acutely and chronically induced in tail suspended rats; interestingly, renal CYP4A1 was also found to be induced (Brunner et al, 2000). Hepatic cytochromes, CYP2E1 and 2C11, were significantly decreased in early to middle tail suspension experiments; these findings support previous experiments in rats on Cosmos 1887 which showed significantly decreased overall CYP expression in the liver (Merrill et al, 1990). While extrapolation between humans and animals in the area of enzymes of drug/xenobiotic metabolism is often problematic since rates of metabolism and enzyme specificity are species specific, the fact that microgravity analog induces changes in rat cytochromes indicates that such changes may be present in humans as well.

6. Increased hematocrit, fluid shifts, and protein binding

Increases in hematocrit are more complex to interpret with regard to drug pharmacokinetics. Increases in hematocrit can be caused by either an increase in red blood cell count or a decrease in plasma volume. Many drugs are bound to red blood cells and an increase

in the red blood cell count can reduce the amount of drug freely dissolved in plasma, thereby reducing the drug's ability to exert therapeutic activity. Reduced plasma volume, however, may cause increased drug binding to red blood cells. Drugs are designed on Earth to have dosing regimens that are based on both volume of distribution as well as particular clearance properties (Gibaldi & Perrier, 1982); thus, reductions in blood water volume, particularly for those drugs that are dissolved in blood water and not appreciably bound by proteins or dissolved in fat, may affect blood concentrations of administered drug, potentially increasing effectiveness and/or increasing toxicity.

In addition to erythrocytes, drugs are also bound to plasma proteins. Albumin and alpha-1 acid glycoprotein are both the major drug binding proteins in blood, non-specifically binding acids and bases respectively. Only a free, or unbound, drug is available to exert therapeutic activity; thus, alterations in concentrations of proteins which bind drugs ultimately may alter the amount of drug available to exert a therapeutic, or toxic, effect. Albumin has been shown to be altered during spaceflight (Guseva & Tashpulatov, 1979). Alpha-1 acid glycoprotein has been shown to decrease (but not in a statistically significant fashion) during spaceflight (Fischer et al, 1972). Whether the elevation of these proteins is due to up-regulation of production, down-regulation of destruction, or simply due to a reduction in the volume of water in which they are suspended is not known.

G. Hypobaria, EVAs, and drug pharmacokinetics

Pressurization of suits, vehicles, and habitats is a requirement for survival in space and on other planetary surfaces. These pressurized environments are not necessarily pressurized to Earth’s sea level atmosphere; instead, configuration of pressurized gas environments is dependent on mission requirements and operational limitations relating to transportation, stowage, and regeneration of gasses. In addition, the pressurization conditions may be different between various spacecraft, habitats, or missions. For example, EVAs currently require a period wherein EVA crewmembers camp out in airlocks pressurized equivalent to high altitudes on Earth (10.2 psi), then don protective suits that are pressurized to less than that (5.7-3.5 psi). Future excursions on planetary surfaces similar to EVAs will require low pressure suits as well.

Acute and chronic exposures to high altitudes, one example of a hypobaric environment, induce physiological changes which affect the pharmacokinetics, and potentially the effectiveness, of some drugs. Red blood cell production increases in hypobaric environments, an adaptation which improves oxygen uptake and transport. Since many drugs are bound to the surfaces of erythrocytes, changes in erythrocyte number and mass lead to alteration in the pharmacokinetics of drugs. The pharmacokinetics of three drugs which are bound to erythrocytes, meperidine, acetazolamide, and prednisolone, have been shown to be altered by acute and chronic exposure to high altitudes. Total clearance of meperidine, an opiate analgesic which is bound to erythrocytes, was decreased and the mean residence time, a pharmacokinetic parameter similar to the half-life, was increased at high altitude, a change which was attributed to an increase in erythrocyte binding, which increased from 41% at sea level to 50.9% after a 10 month stay at high altitude (Ritschel et al, 1996). From a clinical perspective, decreases in clearance can result in prolonged effects, both therapeutic and toxic. Ritschel (et al, 1998a, b) also found changes in the pharmacokinetics of acetazolamide, a drug used to treat altitude sickness and therefore of importance to NASA, after chronic exposure to high altitude. Binding of acetazolamide to erythrocytes increased and to proteins in plasma decreased; the changes in

binding of acetazolamide resulted in an increased clearance and decreased volume of distribution each of which can reduce the efficacy of the drug. The binding of prednisolone, a synthetic glucocorticoid, to erythrocytes increased from 54% at sea level to 75 and 94% in acute and chronic high altitude exposure which increased the maximum concentration and AUC in blood, but not in plasma. These changes resulted in decreased volume of distribution and clearance (Arancibia et al, 2005). Thus, the clinical implications of increased erythrocyte binding induced by hypobaria, such as occurs in EVA, are unique to each drug and a result of the individual properties of each drug.

Changes in pharmacokinetics of drugs due to hypobaria is not limited to drugs bound to erythrocytes and have been demonstrated with furosemide, caffeine, and indocyanin green (Arancibia et al, 2004; Kamimori et al, 1995). Other drugs which may have altered pharmacokinetics, such as due to changes in cytochrome mediated drug metabolism (Streit et al, 2005), after acute or chronic exposure to hypobaria is unique to each drug.

In addition to its effects on pharmacokinetics, hypobaria may alter drug effectiveness by altering pharmacodynamic response. Vaccari (et al, 1978) demonstrated alterations in brain neurotransmitter function, specifically of catecholamines, including serotonin, in adults exposed to high altitudes suggesting that long term excursions in low pressure suits on planetary surfaces may result in altered brain chemistries. Astronauts on Lunar and Martian missions will have many, long-duration (10-12 h) EVAs in suits over the course of each week, and return to vehicles or habitats with different pressurizations and gas contents. The lack of knowledge about the pharmacokinetics of drugs in these non-Earth conditions, and the combined effects of hypobaria, polypharmacy, and the potential for drug interactions, constitutes a gap in the knowledge of drug effectiveness.

H. Drug interactions and therapeutic index

In addition to effects of spaceflight and spaceflight analogs like head down tilt bed rest on the bioavailability of drugs, other factors can affect drug bioavailability such as drug-drug interactions and drug-food interactions. Drug-drug interactions can occur through interactions at the site of absorption into the body by physiochemical processes between either the two drugs or their excipients (Feldman & Hendrick, 1983), through pharmacokinetic interactions once absorbed (such as interactions of metabolism by competition, inhibition, or induction of enzymes of metabolism; Aszalos, 2007; Sills & Brodie, 2007; Zhou, 2006), or through pharmacodynamic interactions at target receptors at the site of action or at the site of toxicity (competition, inhibition, induction, etc; Gan, 2006, El-Masri, 2007). Many drugs can affect one or more of these phenomena and concomitant use of medications can cause changes in therapeutic activity and unexpected therapeutic toxicity.

Drug-drug interactions can occur at various levels. Pharmacokinetic drug-drug interactions result from interaction at the level of absorption, distribution, metabolism, or excretion. Cytochrome mediated pharmacokinetic drug-drug interactions are the most commonly studied of all drug-drug interactions and arise from either induction or inhibition of the cytochromes responsible for the metabolism of the drugs in question. Induction of cytochromes may occur within several hours or several days of administration of a drug or in the instance of chronic therapy. Inhibition may occur immediately after administration of the inhibiting medication, or may require an unspecified time course before the inhibitory activity occurs. In both cases the induction or inhibition activity and its time course is medication specific. Other forms of

pharmacokinetic drug-drug interactions exist, including, but not limited to, metabolic drug-drug interactions which do not involve cytochromes, drug-drug interactions at the site of drug transport, drug-drug interactions caused by shifts in protein binding. In addition to pharmacokinetic drug-drug interactions, pharmacodynamic and toxicodynamic (TD) drug-drug interactions exist and relate to interactions at the target receptor or in toxicities.

The combined medical kits from Shuttle Orbiter Medical System SOMS 2006, SOMS 2003, ISS 2003, and ISS 2005 have been examined to determine the propensity for drug-drug interactions of two contexts: cytochrome mediated pharmacokinetic drug-drug interactions and synergism/antagonism of therapeutic effect based on drug class. In addition to medications in the formularies, analgesics, antibiotics, antidepressants, cardiovascular, and somnolent medications as well as lifestyle drugs (tobacco, St. John's Wort) are also candidates for eliciting untoward therapeutic interactions and there is prevalence of concurrent use of these during spaceflight. In addition, changes in physiology caused by spaceflight may produce as yet unknown drug-drug interactions representing a knowledge gap of unanticipated drug-drug interactions during spaceflight.

Drug-drug interactions have been reported for drug combinations which are operationally relevant to spaceflight. Promethazine, a veteran medication used dually as motion sickness prophylaxis and as a somnolent, is commonly used during spaceflight. Midodrine has also recently been used to combat orthostatic intolerance on return to ground from flight. When co-administered in ground based clinical research, promethazine and midodrine have been found to cause akathesia, a syndrome characterized by anxiety, dysphoria, and malaise (Platts et al, 2006).

A second drug-drug interaction, between dextroamphetamine and scopolamine, has also been discovered. The Reduced Gravity Office utilizes modified aircraft (KC-135, DC-9) to perform parabolic flight, as a simulation environment for freefall for astronaut training and equipment testing. Parabolic flight causes profound motion sickness requiring prophylactic treatment with scopolamine and dextroamphetamine. Flight surgeons anecdotally reported that scopolamine appeared to be less effective on some flights at suppressing motion sickness than on others, potentially due to the common practice of repackaging scopolamine and dextroamphetamine together into gel caps, or potentially due to drug-drug interaction. In a controlled four way cross-over study, it was determined that co-administration with dextroamphetamine reduces the bioavailability of scopolamine, possibly through competing methods of absorption in the GI tract (Boyd et al, 2007). In terms of clinical effects, this interaction could mean a reduced ability of scopolamine to treat symptoms of SMS. This study illustrates the potential for unknown drug interactions that may exist when drugs are used in fashions that are uncommon in standard clinical practice. It is possible that other drugs can be affected similarly by co-administration of dextroamphetamine and have reduced drug absorption and, therefore, reduced efficacy. This combination of scopolamine and dextroamphetamine has been available to astronauts on most Space Shuttle and ISS missions and both are commonly used medications, especially on days of EVA. The potential for dextroamphetamine to interact by reducing absorption of co-administered drugs, particularly tertiary amines like scopolamine, should be considered during mission critical situations.

I. Drug stability and pharmacotherapeutics

Several reasons have been suggested for treatment failure during spaceflight. Alterations in physical or chemical stability of a formulation can result in reduced potency (Cartensen, 1974). Most stability studies concentrate on the amount of active pharmaceutical ingredient (as indexed by loss of potency) as the major determinant of shelf life. Generally, 90% of label claim is considered as the lowest acceptable value of potency. Therefore, for many pharmaceuticals, an estimation of the time that will elapse (when it is stored under specified conditions) before the potency is less than 90% of label claim is considered as the shelf life. However, for certain drug products, safety considerations are of equal or greater importance than shelf life if the degradation products are toxic. Many factors affect stability of a pharmaceutical product such as stability of the active ingredient(s), the potential interaction between the active ingredient and excipients or inactive ingredients, the manufacturing process, the dosage form, the container/closure system, environmental conditions during shipment, storage/handling, and the length of time between manufacture and usage. Environmental factors such as heat, light and moisture and chemical factors like the pH, oxidation, reduction, hydrolysis, or racemization, can all play a vital role in the degradation process.

The effects of most physicochemical factors on drug stability have been well documented and many formulations have been designed to compensate for these effects on Earth. However, the unique environment of space presents certain challenges for assuring drug stability that not have been anticipated during formulation development for conventional use on Earth. The orbiter environment has been known to vary in temperature during the course of a mission with observed temperatures as high as 86^{o}F being recorded during STS-41. Typically elevations in temperature are more common in the Space Shuttle flight deck and occur less frequently in the Space Shuttle middeck where the stowage lockers containing the pharmaceuticals are located. In addition, fluctuations in temperature are typically short in duration and small in magnitude inside the orbiter. The environment on-board the ISS may be more likely to present a humidity-related problem for stability of pharmaceuticals. Experience from orbiting platforms such as Skylab and Mir reveals that ambient humidity fluctuations may be of significant magnitude and duration to impact the stability of some drugs contained in the space medicine kits. Specifications for the internal operational environment for Skylab allowed for a relative humidity of 25-85%. Relative humidity on Mir was to range between 30 to 70%. Long-term exposure to elevations in humidity could have significant adverse effects on some pharmaceuticals. Importantly, cyclic variations in humidity, particularly when combined with elevations in ambient temperature, may impart physical stress on compacted tablets thereby weakening their structure. Alterations in the hardness or compaction of solid dosage forms may significantly affect dissolution and disintegration following oral administration resulting in a change in bioavailability.

Photolytic degradation of drugs by exposure to the low energy of visible light is also a well-documented phenomenon. Many antibiotics are extremely sensitive to exposure to ultraviolet (Maki and Sako, 1977; Matsumoto, et al, 1992a, b) and fluorescent light (Parks, 1985). Light is destructive to such a variety of drug classes that amber bottles are standard for the dispensing of most dosage forms of pharmaceuticals. While amber colored bottles are effective in protecting drugs from the destructive exposure to components of visible light, there are other forms of radiation that may impact the stability of drugs.

The concept of radiation-induced chemical degradation has been suggested in numerous studies in the literature, although little systematic research has been done in this area. Low dose

gamma radiation is used to sterilize some medications and has been found to have minimal effect on drug content (Barbarin, et al, 2001; Maggi et al, 2002). The effects of ^{60}Co-irradiation are the most widely described since exposure to this form of gamma radiation has been used for terminal sterilization of drug products. Corticosteroids, particularly hydrocortisone, show susceptibility to ^{60}Co-irradiation (Kane & Tsuji, 1983). Ahrabi (et al, 1999) demonstrated that thermal neutron irradiation could degrade, in a dose-dependent manner, excipients used in some enteric-coated drug formulations. While low dose gamma radiation is used to sterilize some drugs, exposures to gamma radiation outside the Earth's magnetosphere, such as on the lunar or Martian surfaces, or in Martian orbits of supply vehicles prepositioned for long-duration missions, will be higher than sterilizing exposures.

Other types of radiation are encountered in the space program. Ionizing radiation, from exposure to galactic cosmic rays, solar particle events, trapped particles in the magnetosphere and associated with polar orbit or with the South Atlantic Anomaly, and from daughter ions from structural materials of spacecraft, is associated with extremely high energies/nucleon (NCRP Report #98, 1989; Benton & Benton, 1999, 2001), which may be very destructive to certain classes of drugs. Drugs sterilized by exposure to gamma radiation have yielded some information on the effects of this form of radiation on drug stability (Barbarin, et al, 2001, Maggi et al, 2002), and suitable shielding can be designed to protect drugs from most gamma ray-induced degradation.

V. Computer-based Simulation Information

This section is not applicable to this risk.

VI. Risk in Context of Exploration Mission Operational Scenarios

Medication use has been a part of the NASA manned spaceflight program since its inception. With the increase in mission length and the incidence of illnesses requiring medical intervention; medication use is logically expected to increase. Future exploration class missions will be farther from Earth, and gaps in communication between crews and Earth will require autonomous medical intervention by crewmembers. Exploration class missions are likely to have unique dangers related to exploring planetary surfaces, building habitats, surveying, and maintenance of equipment distal from habitats. Adaptation to reduced gravity may cause an increase in trauma and bone fractures. Despite the highly cross-trained nature of future crews, due to the distance, duration, and configuration of missions, loss or incapacitation of one crewmember will be extremely critical to attainment of mission objectives. Therefore, the availability of safe and effective medications is critical to meet mission objectives.

Failure to provide effective pain medications is not perceived to be a problem for most people, but failure to provide safe and effective pain medications to a patient with a broken leg can result in further complications. Failure to provide safe and effective antibiotics, anesthesia, cardiovascular, or life support medications can be lethal. In the context of extended duration missions at vast distances from Earth and small crew compliment, failure in medications has a potential to negatively impact mission objectives.

VII. Gaps

The Science Advisory Team (SAT) within the Human Health & Countermeasures (HCC) Program Element of the Human Research Program has identified 10 information gaps related to the Risk of Therapeutic Failure Due to Ineffectiveness of Medications. Six of these gaps were identified to be jointly owned by the Pharmacotherapeutics Discipline and Space Medicine Division.

1. Inadequate tracking of medication use, indication, efficacy and side effects.

2. What drug interactions of medications used for levels 2-4 of medical care will adversely affect clinical care?

3. What training methods and reference documents should be employed for training the crew and medical team to identify and mitigate side effects and interactions of commonly used medications?

4. What diagnostic, therapeutic and laboratory technologies are necessary to predict and manage medication side effects, interactions and toxicity during spaceflight?

5. Therapeutic Drug Monitoring in-flight is not capable with current technology.

6. Develop standard procedures for prospective analyses of drugs considered for flight and periodic analyses of drugs that are used for flight.

7. What are the effects of spaceflight on Pharmacokinetics/Pharmacodynamics (PK/PD)?

8. What better ways can be found to administer drugs to provide more rapid and reliable treatment with minimal side effects (intranasal, micro encapsulation, drug cocktails)?

9. What is the effect of long-term spaceflight on drug stability and what measures can be employed to extend the duration of drug efficacy?

10. What are the performance effects of in-flight drugs on exercise, orthostatic tolerance, motor control, cognitive function, etc.?

VIII. Conclusion

Safe and effective pharmacotherapeutic practice is critical to astronaut health and mission success during long-duration space and exploratory missions. All earlier studies with astronaut volunteers during spaceflight indicate that absorption, bioavailability, and pharmacokinetics are affected during spaceflight in ways that reduce efficacy, such as increasing the time to maximum concentrations in the blood, of at least some drugs. However, most of these studies are plagued with inadequate data and control of confounding factors. Future research must address these factors so that definite conclusions can be drawn from both ground-based and in-flight studies.

Anecdotal evidence in the form of opinions of physicians in the Space Medicine Division, personal anecdotal reports of some astronauts, and sparse literature support indicating reduced efficacy, or altered therapeutic or side effects, of medications during spaceflight; this observation

has been partially supplemented by analysis of an incomplete medication use and efficacy data compiled from postflight, but not real-time, medical debriefs database. The limited and compromised results during flight, coupled with the extensive on-board formulary and polypharmacy practice in space, presents a serious gap of knowledge on clinically significant PK/PD of drugs, drug interactions that can potentiate or inhibit pharmacological activity of candidate drugs in the formulary and other related physiological changes that can modify pharmacotherapeutics in space. All operationally relevant drug interactions must be identified carefully, both by literature review and by conducting specific drug interactions research, to assure safe and effective treatment for astronauts on future missions.

Preliminary exploratory investigations into the stability of drugs flown for use by astronauts in space has indicated that some drugs are unstable during spaceflight. More recent results from a payload experiment indicated that the percent of medications with degradation was higher on ISS than on a corresponding Space Shuttle flight. Radiation dose on the ISS was also greater than that on the Space Shuttle in addition to the length of stay of the medications aboard the spacecraft.

Spaceflight analog studies on the ground have given mixed results, but, some studies indicate reduction in oral bioavailability during head down tilt bed rest. Results from carefully designed and controlled flight and ground analog studies are needed to characterize PK/PD and drug interactions that will affect treatment efficacy and safety of medications on board spaceflights. Results from such studies can eliminate ambiguity and identify alterations in PK/PD in reduced gravity environments allowing mitigation and countermeasure development strategies to improve astronaut safety and ensure mission success. Where possible, PK/PD models and drug degradation models using research results from ground-based analog environments, similar to the ones constructed for acetaminophen, will be compiled to help optimize in-flight research results and to predict and develop risk mitigation strategies of pharmacotherapeutics.

IX. References

Aldercreutz H, Pulkkinen MO, Hamalainen EK, Korpela JT. Studies on the role of intestinal bacteria in metabolism of synthetic and natural steroid hormones. Journal of steroid biochemistry. 1984; 20:217-229.

Ahrabi SF, Sande SA, Waaler T, Graffner C. Effects of thermal neutron irradiation on some potential excipients for colonic delivery systems. Drug development and industrial pharmacy. 1999; 25(4):453-462.

Amidon GL, DeBrincat GA, Najib N. Effects of gravity on gastric emptying, intestinal transit and drug absorption. Journal of clinical pharmacology. 1991; 31(10): 968-73.

Arancibia A, Gai MN, Chávez J, Paulos C, Pinilla E, González C, Villanueva S, Ritschel WA. Pharmacokinetics of prednisolone in man during acute and chronic exposure to high altitude. International journal of clinical pharmacology & therapeutics. 2005; 43(2):85-91.

Arancibia A, Nella Gai M, Paulos C, Chávez J, Pinilla E, Angel N, Ritschel WA. Effects of high altitude exposure on the pharmacokinetics of furosemide in healthy volunteers. International journal of clinical pharmacology & therapeutics. 2004; 42(6):314-20.

Aszalos A. Drug-drug interactions affected by the transporter protein, p-glycoprotein (ABCB1, MDR1): II. Clinical aspects. Drug discovery today. 2007; 12(19-20):838-843.

Bagian JP, Ward DF. A retrospective study of promethazine and its failure to produce the expected incidence of sedation during spaceflight. Journal of clinical pharmacology. 1994; 34(6):649-51.

BarBarin N, Tilquin, de Hoffmann E. Radiosterilization of cefotaxime: investigation of potential degradation compounds by liquid chromatography – electrospray mass spectrometry. Journal of chromatography A. 2001; 929:51-61.

Bartelloni PJ, Burchard EC, Hoffler GW, LaPinta CK, Nicogossian AE. Apollo-Soyuz test project. http://lsda.jsc.nasa.gov/scripts/experiment/exper.cfm?exp_index=408

Benton ER, Benton EV. Space radiation dosimetry in low-Earth orbit and beyond. Nuclear instruments and methods in physics research b. 2001; 184(1-2):255-94.

Benton ER, Benton EV. NASA Contractor's Report-1999-209256, Marshall Spaceflight Center, AL, 1999.

Bihl G, Meyers A. Recurrent renal stone disease-advances in pathogenesis and clinical management. Lancet. 2001; 358(9282):651-6.

Blomqvist CG, Nixon JV, Johnson RL Jr, Mitchell JH. Early cardiovascular adaptation to zero gravity simulated by head-down tilt. Acta Astronautica. 1980; 7(4-5):543-553.

Bond JH Jr, Levitt MD, Prentiss R. Investigation of small bowel transit time in man utilizing pulmonary hydrogen (H_2) measurements. Journal of laboratory and clinical investigation. 1972; 85(4):546-55.

Borghi L, Meschi T, Amato F, Novarini A, Romanelli A, Cigala F. Hot occupation and nephrolithiasis. Journal of urology. 1993; 150(6):1757-60.

Boyd JL, Shah V, Wang Z, Vaksman Z, and Putcha L, "Absorption and pharmacokinetics of

acetaminophen in astronauts," American College of Clinical Pharmacology Annual Meeting, September 11, 2005a, Rockville, Maryland.

Boyd J, Wang Z, Putcha L. Effect of sampling schedule on pharmacokinetic parameter estimates of promethazine in astronauts. Journal of Gravitational Physiology, 2005b, 12 (1): P283-4.

Boyd JL, Du B, Vaksman Z, Locke JP, Putcha L. Relative Bioavailability of Scopolamine Dosage Forms and Interaction with Dextroamphetamine. NASA technical brief 20070016002. 2007.

Brunner LJ, Bai S, Abdus-Salaam H. Effect of simulated weightlessness on phase II metabolism in the rat. Aviation, space, & environmental medicine. 2000; 71(9):899-903.

Carmel R, Perez-Perez GI, Blaser MJ. Helicobacter pylori infection and food-cobalamin malabsorption. Digestive diseases and sciences. 1994; 39(2):309-14.

Carstensen JT. Stability of Solids and Solid Dosage Forms, Journal of pharmaceutical sciences. 1974; 63(1):1-14.

Cintrón NM, Putcha L. Pharmacokinetics in flight, Chapter 25 in Space Biology and Medicine Vol III: Humans during spaceflight, Book 2; American Institute of Aeronautics and Astronautics, Reston, VA, 1996, pp. 547-57.

Cintrón NM, Putcha L, Vanderploeg JM. In-flight pharmacokinetics of acetaminophen in saliva. NASA Technical Memorandum 58280, 1987a, 19-23.

Cintrón NM, Putcha L, Vanderploeg JM. In-flight salivary pharmacokinetics of scopolamine and dextroamphetamine. NASA Technical Memorandum 58280, 1987b, 25-29.

Clark J. NSBRI Bioastronautics Investigator's Workshop. Podium. February 2005.

Clements JA, Heading RC, Nimmo WS, Prescott LF. Kinetics of acetaminophen absorption and gastric emptying in man. Clinical pharmacology & therapeutics, 1978, 24(4): 420-31.

Clermont G, Bartels J, Kumar R, Constantine G, Vodovotz Y, Chow C. In silico design of clinical trials: a method coming of age. Critical care medicine, 2004, 32 (10): 2061-70.

Covington TR. Nonprescription drug therapy: issues and opportunities. American journal of pharmaceutical education. 2006; 70(6):137.

Cunningham W. The All-American Boys. New York: Macmillan, 1977.

Davis LE, Neff CA, Baggot JD, Powers TE: Pharmacokinetics of chloramphenicol in domesticated animals. American journal of veterinary research. 1972; 33(11):2259-2266.

Derendorf H. Pharmacokinetic/pharmacodynamic consequences of spaceflight. Journal of clinical pharmacology. 1994; 34(6):684-91.

Diedrich A, Paranjape SY, Robertson D. Plasma and blood volume in space. American journal of medical science. 2007; 334(1):80-5.

Drusano GL. Optimal sampling theory and population modelling: application to determination of the influence of the microgravity environment on drug distribution and elimination. Journal of clinical pharmacology. 1991; 31(10):962-7.

Elfström J, Lindgren S. Influence of bed rest on the pharmacokinetics of phenazone. European journal of clinical pharmacology. 1978; 13(5):379-83.

El-Masri, HA. Experimental and mathematical modeling methods for the investigation of toxicological interactions. Toxicology and applied pharmacology. 2007; 223(2):148-54.

FDA, United States Food and Drug Administration. Dose Selection in Antimicrobial Drug Development Incorporation of Pharmacokinetics and Pharmacodynamics, Rockville, MD, 1999a.

FDA, United States Food and Drug Administration. Guidance for Industry: Population Pharmacokinetics, CP1. Rockville, MD, 1999b.

FDA, United States Food and Drug Administration. Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. Rockville, MD, 1999c.

Feldman S, Hendrick W. Antacid effects on the gastrointestinal absorption of riboflavin. Journal of pharmaceutical sciences. 1983; 72(2):121-123.

Fischer CL, Gill C, Daniels JC, Cobb EK, Berry CA, and Ritzman SE. Effects of spaceflight environment on man's immune system: I. Serum proteins and immunoglobulins. Aerospace Medicine. 1972; 43(8):856-859.

Fukao A, Komatsu S, Tsubono Y, Hisamichi S, Ohori H, Kizawa T, Ohsato N, Fujino N, Endo N, Iha M. *Helicobacter pylori* infection and chronic atrophic gastritis among Japanese blood donors: a cross-sectional study. Cancer causes control. 1993; 4(4):307-12.

Gan TJ. Pharmacokinetic and pharmacodynamic characteristics of medications used for moderate sedation. Clinical pharmacokinetics. 2006; 45(9):855-69.

Gandia P, Bareille MP, Saivin S, Le-Traon AP, Lavit M, Guell A, and Houin G. Influence of simulated weightlessness on the oral pharmacokinetics of acetaminophen as a gastric emptying probe in man: a plasma and a saliva study. Journal of clinical pharmacology. 2003; 43(11):1235-43.

Genin AM. Laboratory simulation of the action of weightlessness on the human organism (NASA TM 75072) 1977. Translated from the Russian.

Gibaldi M,Perrier D. Pharmacokinetics, 2nd ed. Marcel Dekker, New York, 1982.

Gobburu JVS, Marroum PJ. Utilisation of pharmacokinetic-pharmacodynamic modelling and simulation in regulatory decision-making. Clinical pharmacokinetics. 2001; 40(12):883-92.

Graebe A, Schuck EL, Lensing P, Putcha L, Derendorf H. Physiological, pharmacokinetic, and pharmacodynamic changes in space. Journal of clinical pharmacology. 2004; 44(8):837-53.

Grigoriev AI, Huntoon CL, Morukov BV, Lane HW, Larina IM, Smith SM. Endocrine, renal, and circulatory influences on fluid and electrolyte homeostasis during weightlessness: a joint Russian-U.S. project. Journal of gravitational physiology. 1996; 3(2):83-6.

Groza P, Bordeianu A, Boca A. Modifications of the digestive tract in rats subjected to an orbital flight aboard the soviet satellite Kosmos-1129. Physiologie. 1983; 20(1):35-44.

Guseva EV, Tashpulatov RY. Blood albumin-globulin makeup in the crew of the Saliut-3 orbital station. Kosmicheskaya biologiya aviakosmicheskaya meditsina. 1979; 13(3):15-8. (in Russian)

Hawkins WR, Ziegleschmid JF. Clinical aspects of crew health. In Biomedical Results of Apollo (NASA SP 368), Eds. R Johnston, L Dietlein, C Berry. Washington, DC: NASA, 43–81,

1975.

Husebye E. The pathogenesis of gastrointestinal bacterial overgrowth. Chemotherapy. 2005; 51(suppl 1):1-22.

Holgate AM, Read NW. Relationship between small bowel transit time and absorption of a solid meal, influence of metaclopramide, magnesium sulfate, and lactulose. Digestive diseases and sciences. 1983; 28(9):812-9.

Hunt JN, Spurell WR. The pattern of emptying of the human stomach. Journal of physiology. 1951; 113(2-3):157-68. 1978, 348.

Ilett KF, Tee LBG, Reeves PT, Minchin RF: Metabolism of drugs and other xenobiotics in the gut lumen and wall. Pharmacology & therapeutics. 1990; 46(1):67-93.

Kakurin LI, Lobachik VI, Mikhalov VM, Senkevich YA. Anti-orthostatic hypokinesia as a method of weightlessness simulation. Aviation, space, environmental medicine.1976; 47(10):1083-6.

Kamimori GH, Eddington ND, Hoyt RW, Fulco CS, Lugo S, Durkot MJ, Brunhart AE, Cymerman A. Effects of altitude (4300 m) on the pharmacokinetics of caffeine and cardio-green in humans. European journal of clinical pharmacology. 1995; 48(2):167-70.

Kane MP, Tsuji K. Radiolytic degradation scheme for ^{60}Co-irradiated corticosteroids. Journal of pharmaceutical sciences. 1983; 72(1):30-35.

Karnes WE Jr, Samloff IM, Siurala M, Kekki M, Sipponen P, Kim SW, Walsh JH. Positive serum antibody and negative tissue staining for *Helicobacter pylori* in subjects with atrophic body gastritis. Gastroenterology. 1991; 101(1):167-74.

Kates RE, Harapat SR, Keefe DL, Goldwater D, Harrison DC. Influence of prolonged recumbency on drug disposition. Clinical, pharmacology and therapeutics. 1980; 28(5):624-8.

Kingsbury SJ, Yi D, Simpson GM. Polypharmacology: rational and irrational polypharmacy. Psychiatric services. 2001; 52(8):1033-6.

Kuipers EJ, Uyterlinde AM, Peña AS, et al. Long-term sequelae of *Helicobacter pylori* gastritis. Lancet. 1995; 345(8964):1525-8.

Lane HW, LeBlanc AD, Putcha L, Whitson PA. Nutrition and human physiological adaptations to spaceflight. American journal of clinical nutrition. 1993; 58(5):583-8.

Lathers CM, Charles JB, Bungo MW. Pharmacology in space. Part 1. Influence of adaptive changes on pharmacokinetics. Trends in pharmacological sciences. 1989; 10(5):193-200.

Leach CS, Cintrón NM, Krauhs JM. Metabolic changes observed in astronauts. Journal of clinical pharmacology. 1991a; 31(1):921-7.

Leach CS, Inners DL, Charles JB. Changes in total body water during spaceflight. Journal of clinical pharmacology. 1991b; 31(10):1001-6.

Leach CS, Alfrey CP, Suki WN, Leonard JI, Rambaut PC, Inners D, Smith SM, Lane HW, Krauhs JM. Regulation of body fluid compartments during short-term spaceflight. Journal of applied physiology. 1996; 81(1):105-16.

Levine RR. Factors affecting gastrointestinal absorption of drugs. American journal of digestive diseases. 1970; 15(2):171-88.

Levy CM, Smith F, Longueville J, Paumgartner G, Howard MM. Indocyanine green clearance as a test for hepatic function. Evaluation by dichromatic ear densitometry. Journal of the American medical association. 1967; 200(3):236-40.

Lu SK, Bai S, Javeri K, Brunner LJ. Altered cytochrome p450 and p-glycoprotein levels in rats during simulated weightlessness. Aviation, space and environmental medicine. 2002; 73(2):112-8.

Maggi L, Segale L, Ochoa Machiste E, Buttafava A, Faucitano A, Conte U. Chemical and Physical Stability of Hydroxypropylmethylcellulose Matrices Containing Diltiazem Hydrochloride After Gamma Irradiation. Journal of pharmaceutical sciences. 2002; 92(1):131-141.

Maki Y, Sako M. Photochemical Formation and Degradation of Cephalosporins, Journal of the American Chemical Society. 1977; 99(15):5091-9.

Marangella M. Uric acid elimination in the urine. Pathophysiological implications. Contributions to nephrolrology. 2005; 147:132-48.

Martinez MN, Amidon GL. A mechanistic approach to understanding the factors affecting drug absorption: a review of fundamentals. Journal of clinical pharmacology. 2002; 42(6):620-43.

Matsumoto K, Fujibayashi Y, Arano Y, Wada K, Yokoyama A. 62Cu-labeled bifunctional radiopharmaceuticals with metabolizable ester groups. International journal of radiation applications and instrumentation. Part B. 1992a; 19(1):33-8.

Matsumoto M, Kojima K, Nagano H, Matsubara S, Yokota T. Photostability and biological activity of fluoroquinolones substituted at the 8 position after UV irradiation. Antimicrobial agents & chemotherapy. 1992b; 36(8):1715-9.

McLean AJ, McNamara PJ, du Souich P, Gibaldi M, Lalka D. Food, splanchnic blood flow, and bioavailability of drugs subject to first-pass metabolism. Clinical pharmacology & therapeutics. 1978; 24(1):5-10.

Merrill AH Jr, Hoel M, Wang E, Mullins RE, Hargrove JL, Jones DP, Popova IA. Altered carbohydrate, lipid, and xenobiotic metabolism by liver from rats flown on Cosmos 1887. FASEB Journal. 1990; 4(1):95-100.

Meyer JH, Mayer EA, Jehn D, Gu Y, Fink AS, Fried M. Gastric processing and emptying of fat. Gastroenterology. 1986; 90(5 part 1):1176-87.

Meyer JH, Elashoff J, Porter-Fink V, Dressman J, Amidon GL. Human postprandial gastric emptying of 1- to 3-mm spheres. Gastroenterology. 1988; 94(6):315-25.

Col NF. The impact of risk status, preexisting morbidity, and polypharmacy on treatment decisions concerning menopausal symptoms. The American journal of medicine, 2005 Dec 19; 118 Suppl 12B:155-62.

NCRP. Guidance on radiation received in space activities. NCRP Report No. 98. Bethesda, Maryland: National Council on Radiation Protection and Measurements, 1989.

Negrini R, Savio A, Poiesi C, et al. Antigenic mimicry between *Helicobacter pylori* and gastric

mucosa in the pathogenesis of body atrophic gastritis. Gastroenterology. 1996; 111(3):655-65.

Nicholl CG, Polak JM, and Bloom SR. The hormonal regulation of food intake, digestion, and absorption. Annual review of nutrition. 1985; 5:213-39.

Nicogossian AE. Chronological summaries of United States, European, and Soviet bed rest studies. Washington, D.C. Biotechnology Inc, 1979.

Novak M, Shapiro CM, Mendelssohn D, Mucsi I. Diagnosis and management of insomnia in dialysis patients. Seminars in dialysis. 2006; 19(1):25-31.

Parks OW. Photodegradation of sulfa drugs by fluorescent light. Journal - Association of Official Analytical Chemists. 1985; 68(6):1232-4.

Platts SH, Shi SJ, Meck JV. Akathisia with combined use of midodrine and promethazine. Journal of the American medical association. 2006; 295(17):2000-1.

Putcha L, Berens KL, Marshburn TH, Ortega HJ, Billica RD. Pharmaceutical use by U.S. astronauts on space shuttle missions. Aviation, space, and environmental medicine. 1999; 70(7):705-8.

Putcha L. A simple noninvasive method for determining gastrointestinal function. JSC Research &Technology Annual Report. NASA technical memorandum 104747. p. 1, 1991.

Putcha L, Cintrón NM. Pharmacokinetic consequences of spaceflight. Annals of the New York Academy of Sciences. 1991; 618:615-8.

Putcha L, Tietze KJ, Bourne DW, Parise CM, Hunter RP, Cintrón NM. Bioavailability of intranasal scopolamine in normal subjects. Journal of pharmaceutical sciences. 1996; 85(8):899-902.

Putcha L, Cintrón NM, Vanderploeg JM, Chen Y, Habis J, Adler J. Effect of anti-orthostatic bed rest on hepatic blood flow in man. Aviation, space, and environmental medicine. 1988; 59(4):306-8.

Riordan SM, McIver CJ, Walker BM, Duncombe VM, Bolin TD, Thomas MC. The lactulose breath hydrogen test and small intestinal bacterial overgrowth. American journal of gastroenterology. 1996; 91(9):1795-803.

Ritschel WA, Paulos C, Arancibia A, Pezzani M, et al. Pharmacokinetics of meperidine in healthy volunteers after short- and long-term exposure to high altitude. Journal of clinical pharmacology. 1996; 36(7):610-6.

Ritschel WA, Paulos C, Arancibia A, Agrawal MA, Wetzelsberger KM, Lücker PW. Pharmacokinetics of acetazolamide in healthy volunteers after short- and long-term exposure to high altitude. Journal of clinical pharmacology. 1998a; 38(6):533-9.

Ritschel WA, Paulos C, Arancibia A, Agrawal MA, Wetzelsberger KM, Lücker PW. Urinary excretion of acetazolamide in healthy volunteers after short- and long-term exposure to high altitude. Methods and findings in experimental and clinical pharmacology. 1998b; 20(2):133-7.

Saivin S, Pavy-Le Traon A, Soulez-LaRivière C, Güell A, Houin G. Pharmacology in space: pharmacokinetics. Advances in space biology & medicine. 1997; 6:107-21.

Salazar JA, Poon I, Nair M. Clinical consequences of polypharmacy in elderly: expect the unexpected, think the unthinkable. Expert opinions on drug safety. 2007; 6(6):695-704.

Sanaka M, Kuyama Y, Yamanaka M. Guide for judicious use of paracetamol absorption technique in a study of gastric emptying rate of liquids. Journal of gastroenterology. 1998; 33(6):785-91.

Sandler H. Cardiovascular effects of weightlessness. In: Progress in Cardiology. Vol 6, Edited by Yu, P.N., and Goodwin, J.F., Philadelphia, Lea and Febiger, 1976.

Sandler H, Vernikos J. Inactivity: Physiological effects. New York, Academy Press, 1986.

Santavirta J. Lactulose hydrogen and [14C]xylose breath tests in patients with ileoanal anastomosis. International journal of colorectal disease. 1991; 6(4):208-11.

Shi SJ, South DA, Meck JV. Fludrocortisone does not prevent orthostatic hypotension in astronauts after spaceflight. Aviation, space, & environmental medicine. 2004; 75(3):235-9.

Sills G, Brodie M. Pharmacokinetics and drug interactions with zonisamide. Epilepsia. 2007; 48(3):435-441.

Smirnov KV. Role of the gravitational factor in the development of changes in the digestive system. Leningrad fiziologicheski zhurnal. 1986; 72(4):484-9.

Smirnov KV. Symposium on space gastroenterology. Kosmicheskaya biologiya i aviakosmicheskaya meditsina, 1987, 21 (2): 93-4.

Smith SM, Zwart SR, Block G, Rice BL, Davis-Street JE. The nutritional status of astronauts is altered after long-term spaceflight aboard the International Space Station. Journal of nutrition. 2005; 135(3): 437-43.

Srinivasan RS, Bourne DW, Putcha L. Application of physiologically based pharmacokinetic models for assessing drug disposition in space. Journal of clinical pharmacology. 1994; 34(6):692-8.

Stepaniak PC, Ramchandani SR, Jones JA. Acute urinary retention among astronauts. Aviation space & environmental medicine. 2007; 78 (4 Suppl):A5-8.

Streit M, Göggelmann C, Dehnert C, Burhenne J, Riedel KD, et al. Cytochrome P450 enzyme-mediated drug metabolism at exposure to acute hypoxia (corresponding to an altitude of 4,500 m). European journal of clinical pharmacology. 2005; 61(1):39-46.

Taylor DN, Blaser MJ. The epidemiology of helicobacter pylori infection. Epidemiological reviews. 1991; 13:42-59.

Tietze KJ, Putcha L. Factors affecting drug bioavailability in space. Journal of clinical pharmacology. 1994; 34(6):671-6.

Toes MJ, Jones AL, Prescott L. Drug interactions with paracetamol. American journal of thereapeutics. 2005; 12(1):56-66.

USP 29. United States Pharmacopeia and National Formulary (USP 29-NF 24). Rockville, MD: United States Pharmacopeia Convention; 2005:779-781.

Vaccari A, Brotman S, Cimino J, Timiras PS. Adaptive changes induced by high altitude in the development of brain monoamine enzymes. Neurochemistry research. 1978; 3(3):295-311.

Varis O, Valle J, Siurala M. Is *Helicobacter pylori* involved in the pathogenesis of the gastritis characteristic of pernicious anaemia? Comparison between pernicious anaemia relatives and duodenal ulcer relatives. Scandinavian journal of gastroenterology. 1993; 28(8):705-8.

Veehof L, Stewart R, Haaijer-Ruskamp F, Jong BM. The development of polypharmacy. A longitudinal study. Family practice. 2000; 17(3):261-7.

Vernikos J. Pharmacological approaches. Acta astronautica. 1995; 35(4-5):281-95.

Welling PG. "Effects of gastrointestinal disease on drug absorption." Pharmacokinetic basis for drug treatment. pp. 29-48. Eds Benet LZ, Massoud N, Gambertoglio JG. Raven Press, New York, 1984.

Willems M, Quartero AO, Numans ME. How useful is paracetamol absorption as a marker of gastric emptying? A systematic literature study. Digestive diseases and sciences. 2001; 46(10):2256-62.

Winne D. Influence of blood flow flow on intestinal absorption of xenobiotics. Pharmacology. 1980; 21(1):1-15.

Woodmansey P, Bates TE, Read NW. Effect of psychological stress on fluid and electrolyte transport in the human jejunum. Gut, 1983, 24: A991.

Yuan Y, Chen RS, L'Italien G, Karaniewsky R. Development of a parametric simulation model for forecasting goal-oriented treatment outcomes. Value in health. 2004; 7(4):482-9.

Zhou H. Population-based assessments of clinical drug-drug interactions: qualitative indices or quantitative measures. Journal of clinical pharmacology. 2006; 46(11):1268-89.

X. Team

Lakshmi Putcha, PhD, FCP
Chief Pharmacologist
NASA Johnson Space Center

Alan Gewirtz, MD
NSBRI Team Lead, Hematology & Immunology
University of Pennsylvania

James P. Locke, MD
Flight Surgeon
NASA Johnson Space Center

Terrance A. Taddeo, MD
Flight Surgeon
NASA Johnson Space Center

Jason L Boyd, PhD
Pharmacologist
Universities Space Research Association

Brian Du, PhD
Pharmaceutical Scientist
Wyle

Vernie Daniels, MS, RPh
Research Pharmacist
Wyle

XI. List of Acronyms

ANOVA	Analysis of variance
AUC	Area under curve; plasma drug concentration-time curve
AUR	Acute urinary retention
CEV	Crew Exploration Vehicle
C_{max}	Maximum concentration
DSO	Detailed Supplemental Objective
EVA	Extravehicular activity
FD	Flight days
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GI	Gastrointestinal
HHC	Human Health and Countermeasures
ISS	International Space Station
NASA	National Aeronautics and Space Administration
PD	Pharmacodynamics
PK	Pharmacokinetics
PMZ	Promethazine
PRD	Program Requirements Document
SAT	Science Advisory Team
SLS	Spacelab Life Sciences
SMS	Space motion sickness
SR	Sustained release
STS	Shuttle Transportation System
USP	United States Pharmacopeia
XR	Extended release